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10/579,879	05/17/2006	Francis A. Flomerfelt	4239-64851-02	4862

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EXAMINER	
BOESEN, AGNIESZKA	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,879	FLOMERFELT ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *18-20,33,41 and 49-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,21-40 and 44-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received January 30, 2008.

Election/Restrictions

Applicant's election of group I, claims 1-48 and the species of HIV infection and small inhibitory RNA is acknowledged. Because Applicant elected the species of the small inhibitory RNA, claims 18-20, and 41-43 drawn to inhibitory agents other than small inhibitory RNA are withdrawn because the claims are drawn to the non-elected invention. Claims 18-20 and 41-43 do not recite the elected species of small inhibitory RNA, the amino acid sequence of SEQ ID NO: 6 in claims 19, 20, 42, and 43 represents the species of Uba3 peptide. Thus claims 18-20, 41-33, and 49-66 are withdrawn as being drawn to non-elected invention. Restriction requirement is made FINAL. Claims 1-17, 21-40 and 44-48 are under examination in the present Office Action.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

The information disclosure statement (IDS) submitted on May 17, 2006 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner.

Claim Objections

Claims 1-17, 21-40 and 44-48 are objected to because of the following informalities:

Claims are drawn to a method for improving immune function in a subject comprising inhibiting a SPATIAL activity in a subject. The present specification recites the full name for the acronym SPATIAL (see [0281] below);

> [0281] The resulting cDNA clones were then screened for tissue expression in thymus and other organs. One of these genes, named SPATIAL (Stromal Protein Associated with Thymii And Lymph node), is alternatively spliced to generate two mRNAs in mouse thymus.

However because the name SPATIAL appears to be used only in Applicant's own work and therefore would not be easily recognized by the skilled artisan as the Stromal Protein Associated with Thymii And Lymph node, it is suggested that the acronym be spelled out before the first use of the abbreviation in the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are drawn to a method for improving immune function in a subject comprising inhibiting a SPATIAL activity in a subject. Claims do not recite the active method steps to carry out the present method. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps include a step of administering an agent to a subject. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 21-40 and 44-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims (1-17) are drawn to a method for improving immune function in a subject comprising inhibiting a SPATIAL activity in a subject. Claims (21-37) are drawn to a method of increasing thymocyte number in a subject comprising administering to a subject a therapeutically effective amount of an agent that inhibits a SPATIAL activity. Claims (38-40 and 45-48) are drawn to a method of increasing thymocyte number in a subject comprising administering to a subject a therapeutically effective amount of an agent that interferes with an interaction between SPATIAL and Uba3.

The claims are rejected because the specification does not provide an adequate written description regarding specific structures of the putative agents inhibiting SPATIAL activity or agents having capability to interfere with interaction between SPATIAL and Uba3 (all presently rejected claims).

The present specification describes a variety of presumptive agents that the person skilled in the art could test for the capability to inhibit the activity of SPATIAL and the interaction between SPATIAL and Uba3. The proposed agents that could inhibit the activity of SPATIAL

are: small inhibitory RNA, an anti-sense nucleic acid, a ribozyme, an aptamer, a mirror-image aptamer, an Uba3 peptide, a SPATIAL peptide, an Uba3-specific antibody, or a SPATIAL-specific antibody. The agents that could inhibit an interaction between SPATIAL and Uba3 may be an Uba3 peptide, a SPATIAL peptide, an Uba3-specific antibody, a SPATIAL-specific antibody, an aptamer or a mirror-image aptamer. The listed agents represent a genus of a large number of RNA, DNA, and protein sequences and other molecules of unknown structures, as well as a large number of SPATIAL-specific antibodies that could be useful to detect SPATIAL protein in a Western blot, however they may not necessarily inhibit SPATIAL activity in vivo or in vitro.

The specification provides a structure of an Uba3 peptide and the structure of the SPATIAL protein. However the specification does not provide a structure of a single agent that works as required by the claimed methods, that is an agent that effectively inhibits SPATIAL activity (in vivo or in vitro), or an agent that inhibits the interaction between SPATIAL and Uba3. The SPATIAL protein has been identified by the Applicants as a Stromal Protein Associated with Thymii And Lymph node (Applicant's own publication, Flomerfelt et al. Genes and Immunity, 2000, Vol. 1, p. 391-401). Flomerfelt and Gress (Abstract, American Society of Blood and Marrow Transplantation Meeting, 2002) have generated knock out mice for SPATIAL protein and have shown that the SPATIAL knock out mice show an increased number of thymocytes. The present specification describes methods of generating SPATIAL knock out mice and methods for screening compounds with potential for increasing the thymocyte number. However the specification does not describe an agent that effectively inhibits the activity of SPATIAL resulting in improved immune function or increased number of thymocytes. There is

no teaching in the current or prior art of an agent that effectively inhibits SPATIAL activity or the interaction between SPATIAL and Uba3. Applicants have not shown actual reduction to practice of an agent that inhibits SPATIAL activity. While the specification provides a list of various genuses of possible agents that could be used in the present methods, the specification does not provide chemical structures or specific structural features that would likely be associated with inhibitory activity. Thus in view of the above, it is determined that agents possessing the desired activity required to practice the method are not adequately described and were not known in the art. Thus one skilled in the art would conclude that Applicants were not in possession of the methods of improving immune function comprising inhibiting SPATIAL activity.

[MPEP 2163] An adequate written description of a chemical invention requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.,* 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "without such disclosure, the claimed methods cannot be said to have been described.").

In the present case, without the disclosure of any specific small inhibitory RNA, an anti-sense nucleic acid, a ribozyme, an aptamer, a mirror-image aptamer, an Uba3 peptide, a SPATIAL peptide, an Uba3-specific antibody, or a SPATIAL-specific antibody, it is determined that the presently claimed method has not been adequately described.

The skilled artisan cannot envision the detailed structure of a genus of agents that are contemplated in the invention. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-17, 21-40 and 44-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make, and/or use the invention. Claims are drawn to a method for improving immune function in a subject comprising inhibiting a SPATIAL activity in a subject. Claims are drawn to a method of increasing thymocyte number in a subject comprising administering to a subject a therapeutically effective amount of an agent that inhibits a SPATIAL activity. Claims are drawn to a method of increasing thymocyte number in a subject comprising administering to a subject a therapeutically effective amount of an agent that interferes with an interaction between SPATIAL and Uba3.

The claims are rejected because the specification does not provide an adequate enablement for the claimed methods of increasing an immune function by inhibiting the activity of SPATIAL.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors deemed relevant are those of the amount of direction and the working examples provided, that quantity of experimentation necessary, the (un)predictability of the art, and the breadth of the claims.

The claims broadly encompass a large number of agents that must inhibit the activity of SPATIAL and thereby improve the immune function in a subject. The present specification defines improving of the immune function as:

> [0109] Improving immune function: Increasing or enhancing the quality or condition of the immune system; for example, by increasing the number of thymocytes. Improvement in immune function is a characteristic that is recognized by those of skill in the art. Such improvement may be detected by measuring known markers of immune system function, such as T cell number, or by observing a subject's resistance (or increased resistance) to diseases that are known to afflict persons with immune deficiency (such as opportunistic infection).

The recitation "improving an immune function" encompasses enhancing multiple components of both arms of the immune system, the innate and adaptive immunity. The claims broadly encompass inhibiting the activity of SPATIAL protein and/or gene in vivo in a subject. The specification does not provide working examples of an agent that can successfully inhibit the activity of SPATIAL or an agent that interferes with an interaction between SPATIAL and Uba3 either in vivo or in vitro. The specification contemplates a number of different agents that may be tested for their inhibitory activity and describes methods for screening compounds with potential for increasing the thymocyte number (Examples 8-10 and 19). The specification generally discussed an approach to identify anti-sense SPATIAL oligonucleotides (Examples 13-15) and SPATIAL interfering RNA (Examples 17 and 18). The specification provides working examples characterizing the structures of an Uba3 peptide and the SPATIAL protein (Examples 1). The specification provides working examples of generating and analyzing the phenotypic characteristics of SPATIAL knock out mice (Examples 3-6, and 20). However the specification does not describe an agent that effectively inhibits the activity of SPATIAL resulting in improved immune function or increased number of thymocytes.

The SPATIAL protein has been identified by the Applicants as a Stromal Protein Associated with Thymii And Lymph node (Applicant's own publication, Flomerfelt et al. Genes and Immunity, 2000, Vol. 1, p. 391-401 in IDS of 5/17/2006). Flomerfelt and Gress (Abstract, American Society of Blood and Marrow Transplantation Meeting, 2002 in IDS of 5/17/2006) have generated SPATIAL knock out mice and have shown that the knock out mice have an increased number of thymocytes. There is no teaching in the current or prior art of an agent that effectively inhibits SPATIAL activity or the interaction between SPATIAL and Uba3.

The SPATIAL protein is a transcription factor and has been shown to be a negative regulator of the cell cycle. Thus the inhibition of SPATIAL expression is speculated to result in increased cell proliferation and therefore increased cell number. Any agent that could be positively considered to inhibit the expression of SPATIAL gene or the function of the SPATIAL protein must have the capability to enter either the cytoplasm or both the cytoplasm and the nucleus of a cell.

The current art with regard to the gene silencing through RNA interference teaches that the main obstacle with the in vivo siRNA treatment is the delivery of siRNA in a subject (see Aigner, Journal of Biotechnology, 2006, Vol. 124, p. 12-25). Thus the skilled artisan would be required to conduct an undue amount of experimentation in order to identify the siRNA agents that could successfully inhibit the expression of SPATIAL gene in vivo in a subject. Due to the well known obstacles associated with the delivery of potential inhibitory agents to the subject, it would have been highly unpredictable to conclude that a siRNA that may even be shown to inhibit SPATIAL activity in vitro would also inhibit the SPATIAL activity in vivo. It is noted that Applicants have not provided working examples showing evidence of successfully inhibiting the activity of SPATIAL in vitro.

With regard to SPATIAL specific antibodies, it is noted that the administration of such antibodies to the subject would not necessarily result in the inhibition of SPATIAL activity, because the antibodies would not be able to enter the cell in vivo.

Without sufficient enabling disclosure of an agent that can inhibit the activity of SPATIAL the skilled artisan would be unable to practice the claimed methods with a reasonable expectation of success regardless the type of disease, listed in the present claims.

Regarding in vivo methods, which rely on generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction (MPEP 2164.03).

In conclusion, considering the breadth of the claims, the lack of knowledge in the art of a SPATIAL inhibiting agent, the unpredictability in the art, and the lack of working examples in the specification, the skilled artisan would be required to conduct an undue amount of experimentation in order to accurately determine the agents effectively inhibiting the SPATIAL activity and thereby improving an immune function in an individual.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen, Ph.D./
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648